

S/N 10/727,376

July 28, 2006

**REMARKS**

Applicant would like to thank Examiner Hui for granting a personal interview on July 13, 2006. Applicant explained the present invention and the rejections were discussed including US 5,866,168. Applicant agreed to limit the claims to polyvalent metal compounds of aluminum, magnesium and bismuth. No agreement was reached.

**Claim Rejections – 35 USC § 112**

Reconsideration is respectfully requested of the rejection of claims 17 and 18, now claim 31. The polyvalent metal ions for the polyvalent compounds have been limited to aluminum, magnesium and bismuth. The genesis of the claimed method is attributed to the fact that the conventional therapy of acne, warts and herpes simplex often results in scar formation, page 2, lines 6-14. Applicant discovered that in using the present polyvalent metal compounds for such treatment, there no scars formed in virtually all studies, and in one subject, the scar formed rapidly sloughed off and the lesion was healed. (See pages 6-8, Examples I to IV). Scar formation due to various causes and some related references have been briefly mentioned on page 3, lines 18-26. In view of the above, it is respectfully submitted that the invention as claimed in new claim 31 is enabled. Withdrawal of the rejection is respectfully requested.

The rejection of claims 1-2 and 15-18, now claims 19, 23, 27, 31 and 34 should also be withdrawn due to the limitation of the polyvalent metal compounds to those of aluminum and magnesium for claims 19, 23, and 27; aluminum, magnesium and bismuth for claim 31 and bismuth for claim 34. Ample support in the specification and the Examples provide the required enablement.

**Claim Rejections – 35 USC § 102**

The rejection of former claims 1, 2, 4, 11, 12, and 14-18 as anticipated by US 5,866,168 is now deemed moot in view of the new claims. The use of polyvalent aluminum, magnesium and bismuth for treating acne, rosacea and removing scars is not disclosed in this reference.

S/N 10/727,376  
July 28, 2006

### Claim Rejections - 35 USC § 103

Reconsideration is respectfully requested of the rejection of former claims 1-11, now claims 19-16 and 34, in part, with respect to treating warts and acne as allegedly obvious over Remington's Pharmaceutical Sciences, 18<sup>th</sup> ed., 1990, page 768. Remington teaches salicylic acid as useful in treating warts and acne but is totally silent with regard to the claimed invention which requires polyvalent metal compounds, where a salicylate salt may be used. Prior to the present invention as claimed, salicylic acid salts were deemed inactive in treating various dermatological diseases (see "Drug Treatment, Principles and Practice of Clinical Pharmacology and Therapeutics", edited by G.S. Avery, 1976; page 329). A copy is attached for the convenience of the examiner. In view thereof, the use of polyvalent metal compounds as presently claimed for treating acne and warts, including a salicylate salt, was actually taught against by the prior art thereby rendering the present claims patentable. Withdrawal of the rejection is respectfully requested.

Reconsideration is also respectfully requested of the rejection of former claims 1, 2, 4, 8, and 13 (new claim 19) as allegedly obvious over US 4, 595,591. The '591 patent describes chromium, zinc and copper as known for the treatment of warts. The present claims are limited to aluminum, magnesium and bismuth polyvalent compounds thereby rendering the rejection moot. There is no suggestion in the '591 patent to use the present claimed compounds. The rejection should be withdrawn.


S/N 10/727,376  
July 28, 2006

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD  
P.O. Box 2903  
Minneapolis, Minnesota 55402-0903  
(612) 332-5300

RAD/kek  
Date: July 28, 2006

By:   
Ronald A. Daignault, Esq.  
Reg. No. 25,968



# Drug Treatment

## Principles and Practice of Clinical Pharmacology and Therapeutics

EDITED BY

**Graeme S. Avery**

Editor-in-Chief  
Australian Drug Information Services Pty Ltd  
Sydney • Auckland  
Editor  
Drugs • Clinical Pharmacokinetics

1976



ADIS PRESS, Sydney

PUBLISHING SCIENCES GROUP INC, Littleton, Massachusetts

07/19/2006 08:12 5307899408

## Sect. 1

## Clinical Pharmacological Considerations

329

The ability of a drug applied topically to penetrate the skin satisfactorily may be decreased by scale or crust on the surface of the lesion, although this is not necessarily of great practical importance, and certainly in impetigo there is no evidence that removal of the crusts hastens healing by topical antibiotics. The presence of a de-epithelialised surface increases the absorption of certain topical applications, e.g. boric acid, so that quantities which do not produce toxic effects when applied to intact dry skin do so when the skin is damaged: it is not clear whether this is due to increased blood supply to damaged skin, to presence of exudate on the surface, or to removal of the 'barrier' action of the stratum corneum. However, it is known that when the stratum corneum is removed, penetration of the skin by the majority of substances is enhanced.

There are certain regional differences in absorption of topically applied substances and, in general, absorption is greatest from flexural surfaces: the occlusive effect of apposing surfaces is a factor and local anatomical differences in the skin are also important. It is in the flexures that striae are especially prone to appear after topical corticosteroid therapy. It does not necessarily follow that increased absorption of the corticosteroid is to blame as the mechanical stresses and strains which are great at these sites are known to be important in the production of striae.

### 1.3.2 Stability and Compatibility

Effective stable preparations of certain drugs which would otherwise appear ideal for topical use may not be available for various reasons. Some drugs can be used topically as long as fresh solutions are made up frequently. In other instances, the problem can be solved by adjusting pH, storing at low temperature, keeping in the dark, etc but in some cases the practical difficulties are at the present time insuperable. Some of the commonly used cream bases will not keep for any length of time without becoming contaminated with moulds, and when this particular problem is overcome by adding preservatives, a second potential

problem of contact sensitivity to the preservatives, e.g. parabens or chlorocresol, may arise (see section 12.3.4).

Just as there are 'incompatible' mixtures in internal medication (see chapter VIII), so there are substances which should not be mixed in topical preparations, e.g. salicylic acid combines with zinc to form zinc salicylate which no longer has the effect on the skin of salicylic acid: when dithranol is used in zinc paste the zinc oxide of the paste combines with the dithranol to form an inert compound, though in this case the presence of salicylic acid is helpful in preventing the unwanted interaction between dithranol and zinc. Another undesirable effect of mixing is seen with DMSO, for although it enhances absorption of a number of substances, including steroids, it may reduce the therapeutic effectiveness of certain steroids when it is mixed with them; presumably there is chemical alteration in the steroid.

### 1.3.3 Undesirable Local Effects of Drug When Used Topically

Antihistamines, local anaesthetics (except amides such as lignocaine) and certain antibiotics, including penicillin and streptomycin, are so liable to produce contact dermatitis that they should never be applied to the skin. Consequently, their use in dermatology is restricted to oral or parenteral administration, or in the case of local anaesthetics, to local injections.

Some drugs have an adverse effect on the skin whether given systemically or topically. The deleterious effects of corticosteroids on the skin is a good example, whether they are produced as part of a Cushing's syndrome following systemic administration, or purely as the result of a local effect when applied to the skin directly. In certain diseases (e.g. severe eczema) in which the choice may lie between treatment with a topical or a systemic corticosteroid, it may be that the adverse effects on the skin will prove to be greater with the topical preparation than with the systemic preparation given in the dose required to produce the same therapeutic effect. Thus, in certain special situa-

## Sect. 1

## Clinical Pharmacological Considerations

329

The ability of a drug applied topically to penetrate the skin satisfactorily may be decreased by scale or crust on the surface of the lesion, although this is not necessarily of great practical importance, and certainly in impetigo there is no evidence that removal of the crusts hastens healing by topical antibiotics. The presence of a de-epithelialised surface increases the absorption of certain topical applications, e.g. boric acid, so that quantities which do not produce toxic effects when applied to intact dry skin do so when the skin is damaged: it is not clear whether this is due to increased blood supply to damaged skin, to presence of exudate on the surface, or to removal of the 'barrier' action of the stratum corneum. However, it is known that when the stratum corneum is removed, penetration of the skin by the majority of substances is enhanced.

There are certain regional differences in absorption of topically applied substances and, in general, absorption is greatest from flexural surfaces: the occlusive effect of apposing surfaces is a factor and local anatomical differences in the skin are also important. It is in the flexures that striae are especially prone to appear after topical corticosteroid therapy. It does not necessarily follow that increased absorption of the corticosteroid is to blame as the mechanical stresses and strains which are great at these sites are known to be important in the production of striae.

### 1.3.2 Stability and Compatibility

Effective stable preparations of certain drugs which would otherwise appear ideal for topical use may not be available for various reasons. Some drugs can be used topically as long as fresh solutions are made up frequently. In other instances, the problem can be solved by adjusting pH, storing at low temperature, keeping in the dark, etc but in some cases the practical difficulties are at the present time insuperable. Some of the commonly used cream bases will not keep for any length of time without becoming contaminated with moulds, and when this particular problem is overcome by adding preservatives, a second potential

problem of contact sensitivity to the preservatives, e.g. parabens or chlorocresol, may arise (see section 12.3.4).

Just as there are 'incompatible' mixtures in internal medication (see chapter VIII), so there are substances which should not be mixed in topical preparations, e.g. salicylic acid combines with zinc to form zinc salicylate which no longer has the effect on the skin of salicylic acid: when dibranol is used in zinc paste the zinc oxide of the paste combines with the dibranol to form an inert compound, though in this case the presence of salicylic acid is helpful in preventing the unwanted interaction between dibranol and zinc. Another undesirable effect of mixing is seen with DMSO, for although it enhances absorption of a number of substances, including steroids, it may reduce the therapeutic effectiveness of certain steroids when it is mixed with them; presumably there is chemical alteration in the steroid.

### 1.3.3 Undesirable Local Effects of Drug When Used Topically

Antihistamines, local anaesthetics (except amides such as lignocaine) and certain antibiotics, including penicillin and streptomycin, are so liable to produce contact dermatitis that they should never be applied to the skin. Consequently, their use in dermatology is restricted to oral or parenteral administration, or in the case of local anaesthetics, to local injections.

Some drugs have an adverse effect on the skin whether given systemically or topically. The deleterious effects of corticosteroids on the skin is a good example, whether they are produced as part of a Cushing's syndrome following systemic administration, or purely as the result of a local effect when applied to the skin directly. In certain diseases (e.g. severe eczema) in which the choice may lie between treatment with a topical or a systemic corticosteroid, it may be that the adverse effects on the skin will prove to be greater with the topical preparation than with the systemic preparation given in the dose required to produce the same therapeutic effect. Thus, in certain special situa-